UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/886,227 | 06/21/2001 | Michael Samoszuk | 034827-0201 | 5866 |

30542 7590 06/25/2003

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

| EXAMINER | |
|---|---|
| FREDMAN, JEFFREY NORMAN | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 09/886,227 | SAMOSZUK ET AL. |
| | Examiner | Art Unit |
| | Jeffrey Fredman | 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-18* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The rejection of claim 16 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-5, 7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menke et al (Electrophoresis (1995) 16:733-738) in view of Chen et al (Clinical Chemistry (1999) 45(8):1162-1167).

Menke teaches a method for determining the clonality of a T-cell receptor (TCR) rearrangment in a sample (see abstract) comprising:

(a) extracting nucleic acid from a human, formalin fixed, paraffin embedded tissue specimen or from blood monocytes (white blood cells) (see page 734, column 1, subheading "DNA extraction"),

(b) amplifying said nucleic acid by polymerase chain reaction with two TCR specific primers which amplify the VJ region to provide TCR DNA fragments (See page 734, subheading "PCR" and figure 1),

(c) analyzing said TCR DNA fragments using an electrophoretic gel with urea by temperature gradient gel electrophoresis (TGGE), wherein the presence of one or more discrete bands in said electrophoresis gel indicates the presence of a clonal TCR rearrangement (see page 734, column 2, subheading "gel electrophoresis" to page 735, column 1 and figure 2).

Menke suggests the use of skin biopsy specimens (see page 737, column 2).

Menke teaches the use of DNA migration markers (see page 735, figure 2, pBR 322 HaeIII digest) including positive controls for clonal T-cell rearrangements (see page 735, figure 3).

Menke teaches the use of the method for diagnoses of patients suspected of having lymphoma (see page 737, column 2).

Menke does not teach the use of TTGE in the place of TGGE.

Chen teaches the use of TTGE methods for the analysis of clonality in patients (see page 1163, column 2). Chen expressly motivates the use of TTGE as superior to TGGE (see page 1163, column 2). Chen teaches raising the temperature of the gel in a template dependent manner from temperatures as low as 53 C to as high as 64 C in a

polyacrylamide gel with urea by incrementing the temperature 1.2 degree C/hour over 6 hours at 145 V. With respect to the voltage and temperature range, these are results optimizable variables which the ordinary practitioner recognizes depend upon the specific gel apparatus, concentration of gel. Thus, an ordinary practitioner would have recognized that the results optimizable variables could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific voltages or times was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the TGGE clonal analysis method of Menke by use TTGE in the place of TGGE since Menke recognizes a problem in detection is that "more sensitive electrophoresis techniques are required (page 737, column 1)". Chen provides the solution to this problem, and states "TTGE differs from TGGE, which has been reported several times, in that TGGE has a fixed temperature gradient from top to bottom of the gel. In TTGE, the temperature at any location of the entire gel is the same at any given time but changes with respect to time (temporal temperature). Thus, it is easier to modulate the temperature over time and provide a wider separation range that increases sensitivity (page 1163, column 2)". Chen further notes that "Thus, TTGE is

simple and more cost effective without sacrificing sensitivity (see page 1167, column 1)". An ordinary practitioner, faced with the suggestion of Menke who desired more sensitive electrophoresis techniques and also faced with the desire for cost effectiveness in diagnostic assays, would have been motivated to solve this problem by using the TTGE method of Chen, since Chen expressly teaches that the method is more sensitive than TGGE, and also more cost effective, thereby resolving both concerns of the ordinary practitioner.

4. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menke et al (Electrophoresis (1995) 16:733-738) in view of Chen et al (Clinical Chemistry (1999) 45(8):1162-1167) as applied to claims 1-5, 7 and 9-15 and further in view of Chott et al (J. Invest. Dermatol. (19966) 106(4):696-700).

Menke in view of Chen teach the limitations of claims 1-5, 7 and 9-15 as discussed above.

Menke in view of Chen do not teach comparing two lesions in a patient to determine if the identical clonal T cell rearrangments are present in each sample.

Chott teaches analysis of multiple lesions in the same patients in order to determine if the clonal rearrangments are the same (see abstract and page 698, columns 1 and 2). Chott expressly shows the situation where a patient has recurrences in the same location (see patient 7, page 699, figure 4, with four occurrences on the right forearm) as well as where different loci are present (see patient 11, page 698, table I, with occurrences on leg and back and buttock).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the TTGE method of detection of clonality of T cells of Menke in view of Chen to the multiple lesions studied by Chott since it permits a determination of whether the disease is a clonal disorder as Chott notes "The results offer strong evidence that LyP is a clonal lymphoproliferative disorder and indicate that regressing lesions of LyP are clonally related to the malignant lymphoma of most LyP patients (page 696, column 2)". An ordinary practitioner would have been motivated to determine the clonality of the T cells since this would permit achievement of the goal of Menke, which is "monitoring minimal residual disease under therapeutic conditions (page 737, column 2)" in order to permit "an individualized therapeutic approach in lymphomas (page 737, column 2)". Thus, an ordinary practitioner would have been motivated to apply the method of Menke in view of Chen to the multiple lesion situation of Chott in order to monitor the disease and determine whether the lesion is a regression or is a new lesion in order to individualize the therapeutic approach and increase the success of treatments.

5. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Menke et al (Electrophoresis (1995) 16:733-738) in view of Chen et al (Clinical Chemistry (1999) 45(8):1162-1167) as applied to claims 1-5, 7 and 9-15 and further in view of Theodorou et al (Blood (1995) 86(1):305-310).

Menke in view of Chen teach the limitations of claims 1-5, 7 and 9-15 as discussed above.

Menke in view of Chen do not teach analysis of lymph node samples.

Theodorou teaches the analysis of lymph node samples for clonality of T Cell receptor genes by PCR and DGGE (see page 305, abstract and column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the TTGE method of detection of clonality of T cells of Menke in view of Chen to the lymph node tissue of Theodorou since Theodorou states "The lymph node analysis by PCR showed a predominant T-cell clone in three of four biopsies (see page 309, column 1)". So an ordinary practitioner would have been motivated to analyse lymph node tissue since it would provide effective determination regarding the clonality of the T-cell population and since the analysis permits detection "even when the lymph node sample looks histologically benign (page 309, column 1)".

***Allowable Subject Matter***

6. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. The following is a statement of reasons for the indication of allowable subject matter: Claim 8 is drawn to SEQ ID Nos: 3 and 4 which were not found in the prior art sequence search.

***Response to Arguments***

8. Applicant's arguments filed April 28, 2003 have been fully considered but they are not persuasive.

Applicant cites "Farnleitner" to argue an obviousness rejection which is based upon Menke in view of Chen. The "Farnleitner" reference is not cited in the rejection,

but Applicant argues that the teachings of this reference conflict with Chen, who expressly teaches that TTGE is superior to TGGE, noting "Thus, TTGE is simple and more cost effective without sacrificing sensitivity (see page 1167, column 1)". Chen is replete with strong suggestive power to substitute TTGE for TGGE.

Contrary to Applicant's statement, Farnleitener does not teach that TTGE was unable to separate any of the tested sequences, but could not distinguish equimolar mixtures of single nucleotide polymorphisms. However, this teaching of Farnleitener does not overcome the prima facie case for several reasons. First, the claims are not commensurate in scope with the asserted teaching away by Farnleitener. The claims are not drawn to detection of single nucleotide polymorphisms, but are broadly drawn to detection of any T-cell rearrangements.

Second, other prior art that is aware of the Farnleitener reference notes that for rearrangements, TTGE is superior to DGGE. For example, Shina et al (Letters App. Microbiol. (June 2001) 32:384-387) notes that "In one study, it was concluded that TTGE was less effective than DGGE as a method for the discrimination of sequences with a single base differences (Farnleitner et al. 2000). However, at the level of discrimination required in this study, TTGE provides a relatively simple and effective alternative to DGGE (page 387, column 1)." This prior art reference, while not relied upon in the rejection, would also support the obviousness of the use of TTGE in the place of DGGE. Shina also directly rebuts Applicant's statement that TTGE was not effective, noting that in certain limited cases, TTGE was simply less effective.

Further, other cited art on the IDS supports the desirability of using TTGE. For example Vazquez et al (Lett. Appl. Microbiol. (2001) 32:215-219) also lauds TTGE as a successful method for differential detection (see page 218, column 1, for example). Higashimoto also lauds TTGE, noting "Our preliminary data demonstrate that TTGE is an accurate, rapid, and inexpensive method to detect FCFR mutations in patients with sqlective craniosynostosis syndromes (see page 2006, column 1)". Consequently, far from being a situation where the totality of the prior art teaches away from the use of TTGE, the current situation is one in which TTGE is suggested by an abundance of prior art, most particularly by the cited and relied upon Chen reference.

Third, MPEP 2123 notes "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." So a fortiori, if there is a reference that directly teaches towards the claimed invention, the presence of a single reference which suggests that in limited circumstances one method may be somewhat less effective is not a teaching away.

Applicant then argues this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, Chen shows that TTGE functions such that "**all 104 known mutations were correctly detected** (emphasis mine, page 1167, column 1)." A showing of 104 successes which represents a perfect detection rate is sufficient for a

reasonable expectation of success in applying the method to analysis of TCR mutations as taught by Menke. The successes of Chen do not even include the successes of other references such as Vazquez or Higashimoto or Yoshino using TTGE. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art of Menke desires improvement and Chen directly suggests and teaches substitution of DGGE with TTGE for specific reasons given in the rejection above. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of TTGE with 104 specific successful mutations detected by Chen.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant does not separately argue the dependent claims, and since the independent rejection is maintained, these rejections will also be maintained.

***Conclusion***

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

June 18, 2003